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# TIME COURSE OF SEIZURE-INDUCED CHANGES OF HCN CHANNEL ISOFORM EXPRESSION

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**Rationale:** Experimental prolonged febrile (and kainate-evoked) seizures alter the expression of HCN channels in the hippocampus: one week after the seizures, reduction of HCN1 and enhancement of HCN2 in the hippocampal CA1 and CA3 has been found (Brewster et al., 2002). This regulation of HCN channel expression could be a direct, activity-dependent effect of seizures, or secondary to 'compensatory' phenomena, including increased activation of these hyperpolarization-triggered channels by enhanced GABAergic inhibition (Chen et al., 1999). Because increased IPSC frequency was present at 1 week after seizures but not at 24 hours, we set out to determine the time course of seizure-evoked alteration of HCN expression levels.

**Methods:** Seizures were induced *in vivo* (prolonged experimental febrile seizures) and *in vitro* (low $[Mg^{2+}]$ in organotypic hippocampal slice cultures). HCN1 and HCN2 mRNA expression levels were determined at 24,48 and 72 hours after both *in vivo* and *in vitro* seizures, using semi-quantitative *in situ* hybridization (Brewster et al., J Neurosci, 2002; Bender et al., J Neurosci, 2003) and aRNA single cell analysis.

**Results:** The enduring alterations of HCN1 and HCN2 expression that were found at 1–12 weeks after developmental seizures, were not evident at 24 hours after induction of experimental febrile seizures *in vivo*. This is consistent with the lack of HCN1 and HCN2 changes at the 24 hour point after *in vitro* seizures, where the divergence of HCN1 and HCN2 expression was found by 48 hours. Because these time-course data do not conclusively determine the relationship of enhanced hyperpolarizing drive and HCN channel expression, *in vitro* manipulations of GABA levels and GABAergic activity are currently under way.

**Conclusions:** Changes in HCN channel expression are not present at 24 hours after *in vivo* or *in vitro* seizures, but are found by 48 hours. Whether slow mRNA turnover, or indirect (or compensatory) effects of the seizures underlie these findings is currently under investigation. (Supported by NIH NS 35439; 28912 EFA.)